

1247918

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UNITED STATES DEPARTMENT OF COMMERCE
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November 10, 2004

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: 10/689,015
FILING DATE: *October 20, 2003*
RELATED PCT APPLICATION NUMBER: PCT/US04/34486

Certified by



Jon W Dudas

Acting Under Secretary of Commerce
for Intellectual Property
and Acting Director of the U.S.
Patent and Trademark Office

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UTILITY PATENT APPLICATION TRANSMITTAL <small>(Only for new nonprovisional applications under 37 CFR 1.53(b))</small>		Attorney Docket No. BTI 3.0-002	
		First Inventor Gérald E. Piérard	
		Title METHODS FOR TREATING TRANSEPIDERMAL WATER LOSS	
		Express Mail Label No. EV 342574935 US	

10/689015
 102003

APPLICATION ELEMENTS <small>See MPEP chapter 600 concerning utility patent application contents.</small>	ADDRESS TO: MS Patent Application Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450
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1. <input checked="" type="checkbox"/> Fee Transmittal Form (e.g., PTO/SB/17) <small>(Submit an original, and a duplicate for fee processing)</small> 2. <input type="checkbox"/> Applicant claims small entity status. <small>See 37 CFR 1.27.</small> 3. <input checked="" type="checkbox"/> Specification [Total Pages 27] <small>(preferred arrangement set forth below)</small> <ul style="list-style-type: none"> - Descriptive title of the invention - Cross Reference to Related Applications - Statement Regarding Fed sponsored R & D - Reference to sequence listing, a table, or a computer program listing appendix - Background of the invention - Brief Summary of the invention - Brief Description of the Drawings (if filed) - Detailed Description - Claim(s) - Abstract of the Disclosure 4. <input checked="" type="checkbox"/> Drawing(s) (35 U.S.C. 113) [Total Sheets 2] 5. Oath or Declaration [Total Sheets] <ul style="list-style-type: none"> a. <input type="checkbox"/> Newly executed (original or copy) b. <input type="checkbox"/> Copy from a prior application (37 CFR 1.63(d)) <small>(for continuation/divisional with Box 18 completed)</small> <ul style="list-style-type: none"> i. <input type="checkbox"/> DELETION OF INVENTOR(S) Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b). 6. <input checked="" type="checkbox"/> Application Data Sheet. See 37 CFR 1.76	7. <input type="checkbox"/> CD-ROM or CD-R in duplicate, large table or Computer Program (Appendix) 8. <input type="checkbox"/> Nucleotide and/or Amino Acid Sequence Submission <small>(if applicable, all necessary)</small> <ul style="list-style-type: none"> a. <input type="checkbox"/> Computer Readable Form (CRF) b. Specification Sequence Listing on: <ul style="list-style-type: none"> i. <input type="checkbox"/> CD-ROM or CD-R (2 copies); or ii. <input type="checkbox"/> Paper c. <input type="checkbox"/> Statements verifying identity of above copies
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ACCOMPANYING APPLICATION PARTS	
9. <input type="checkbox"/> Assignment Papers (cover sheet & document(s)) 10. <input type="checkbox"/> 37 CFR 3.73(b) Statement <input type="checkbox"/> Power of Attorney <small>(when there is an assignee)</small> 11. <input type="checkbox"/> English Translation Document (if applicable) 12. <input type="checkbox"/> Information Disclosure Statement (IDS)/PTO-1449 <input type="checkbox"/> Copies of IDS Citations 13. <input type="checkbox"/> Preliminary Amendment 14. <input checked="" type="checkbox"/> Return Receipt Postcard (MPEP 503) <small>(Should be specifically itemized)</small> 15. <input type="checkbox"/> Certified Copy of Priority Document(s) <small>(if foreign priority is claimed)</small> 16. <input type="checkbox"/> Nonpublication Request under 35 U.S.C. 122 (b)(2)(B)(i). <small>Applicant must attach form PTO/SB/35 or its equivalent.</small> 17. <input type="checkbox"/> Other: 	

18. If a CONTINUING APPLICATION, check appropriate box, and supply the requisite information below and in the first sentence of the specification following the title, or in an Application Data Sheet under 37 CFR 1.76:

☐ Continuation
 ☐ Divisional
 ☐ Continuation-in-part (CIP)
 of prior application No.: _____

Prior application information: Examiner _____
 Art Unit: _____

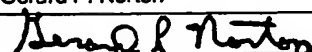
For CONTINUATION OR DIVISIONAL APPS only: The entire disclosure of the prior application, from which an oath or declaration is supplied under Box 5b, is considered a part of the disclosure of the accompanying continuation or divisional application and is hereby incorporated by reference. The incorporation can only be relied upon when a portion has been inadvertently omitted from the submitted application parts.

19. CORRESPONDENCE ADDRESS			
<input checked="" type="checkbox"/> Customer Number: 000530		OR <input type="checkbox"/> Correspondence address below	
Name 			
Address 			
City	State	Zip Code	
Country	Telephone	Fax	

Name (Print/Type)	Gerard P. Norton	Registration No. (Attorney/Agent)	36,621
Signature	<i>Gerard P. Norton</i>	Date	October 20, 2003

17648 U.S. PTO

Use in lieu of PTO/SB/17 (08-03)
(Form updated to reflect FY 2004 fees effective 10/1/03)

FEE TRANSMITTAL for FY 2004		Complete if Known																																																																																																																																																																																																					
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METHODS FOR TREATING TRANSEPIDERMAL WATER LOSS

BACKGROUND OF THE INVENTION

[0001] One important source of moisture in skin is transepidermal water. Transepidermal water is the moisture that migrates upward from deeper dermal tissues to the epidermis, where it hydrates (adds water to) the stratum corneum and then evaporates into the atmosphere. This process is called transepidermal water loss (TEWL).

[0002] Skin maladies and other skin disorders related to increased TEWL and impaired barrier function have plagued mankind for centuries. They range from temporary dry skin caused by environmental conditions to serious illnesses, which can cause incapacitation and death. Included in this range are dry skin, severe dry skin, dermatitis, psoriasis, eczema, xerosis, terosis, dandruff, ichthyosis, epidermolytic hyperkeratosis, axillary hidradenitis suppurativa, infantile seborrheic dermatitis, atopic dermatitis, chronic dermatitis, keratoses, pruritis, age spots, cradle cap, lentigines, scales, melasmas, wrinkles, stretch marks, dermatoses, minor burns and erythema.

[0003] These maladies and disorders can be treated in a number of ways including oral ingestion of drugs, intravenous injection of drugs, dietary modification, topical applications and other therapeutic methods. Of these treatment methods, the one most preferable and convenient to patients is generally a topical application.

[0004] The stratum corneum (SC) barrier function is largely dictated by extracellular lipids consisting of a mixture of ceramides, cholesterol and fatty acids together with smaller amounts of cholesterol sulphate, glucosyl ceramides and phospholipids (Yardley, (1987) Int. J. Cosmet. Sci. 9:13-19; Elias et al., (1988) J. Invest. Dermatol. 91:3-10; Rawlings et al., (1996) Arch. Dermatol. Res. 288:383-390). Skin barrier alterations exhibit profound negative effects on skin

physiology. They may exacerbate some inflammatory dermatoses by inducing or boosting micro-inflammation in the irritation cascade. Measuring the transepidermal water loss (TEWL) is a good means for assessing the SC barrier function (Bashir et al., (2001) Skin Res. Technicol. 7:40-48; Zhai et al., (1998) Int. J. Dermatol. 37:386-389; Rosado and Rodrigues, (2003) Int. J. Cosmet. Sci. 25:37-44). Experimentally, tape strippings compromise the barrier function (Id.) and the recovery rate of TEWL reflects its repair kinetics.

[0005] Measurement of TEWL, based on the estimation of the water vapor gradient in an open chamber, is being used to support claims of cosmetics including product mildness, reduction in irritative skin reactions, skin hydration, skin repair, protective effect against UV damage and others. TEWL measurement can also screen ingredients that have a beneficial effect on the barrier function and offer the possibility to monitor in vivo, on human skin, the effect of topical treatment in an objective and non-invasive way.

[0006] So called barrier creams aim at protecting the skin from various noxious chemical effects. They may also be used as a surrogate of the natural SC function once it is weakened. These topical products tend indeed to make partial occlusion. The real level of efficacy of barrier creams is disputed. Other topical formulations and some ions can help in correcting the excess in TEWL after damaging the SC (Rawlings et al., (1996) Arch. Dermatol. Res. 288:383-390; Denda and Kumazawa, (2002) J. Invest. Dermatol. 118:65-72). Petrolatum is one of the skin barrier surrogates. Petrolatum's moisturizing characteristics have been ascribed to the slowed water loss when applied to the skin. The effect of the addition of zinc oxide (ZnO) to form a paste is unknown on this parameter. No information is also available on the effect of the many pharmacological agents that can be incorporated in pastes.

[0007] Azole derivatives are antimicrobial agents with effects on bacteria, fungi and protozoa. In fact, broad-spectrum antifungal products containing miconazole have been marketed in Europe to treat diaper rash. Although, these products are recommended for treatment of diaper dermatitis when *Candida albicans* is involved in this condition, there has been no teaching or suggestion in the art that miconazole containing products would prevent or ameliorate skin barrier alterations.

[0008] U.S. Patent No. 4,911,932 discloses ointment skin care compositions containing petrolatum, zinc oxide and miconazole nitrate to treat acute inflammatory skin conditions. There is no teaching or suggestion in this patent concerning the use of such skin care compositions for treatment and prevention of TEWL.

[0009] Skin-protective products claiming to be barrier creams should be shields against noxious chemicals. However, the evidence in favor of their clinical usefulness is not compelling and is even contradictory (Pigatto et al., (1992) Contact Dermatitis 2226:197). Several studies have come to the conclusion that the efficacy of most of these products was questionable or even nonexistent. When evidence of efficacy is lacking, it may be due to the dearth of suitable standardized techniques for their evaluation or to the inadequate barrier properties of the preparation (Goffin et al., (1998) Dermatology 196:434-437). There is a need for better skin moisturizing compositions.

SUMMARY OF THE INVENTION

[00010] Applicants have discovered that the addition of azole derivatives to a skin barrier protecting vehicle, increases the skin protective capacity of the vehicle.

[00011] Accordingly, a first aspect of the present invention is directed to azole derivatives that can be formulated into suitable therapeutic, dermatological, pharmaceutical, medical,

and/or cosmetic compositions depending on the particular use for which it is to be used.

[00012] Preferred embodiments of the present invention comprise a combination of at least one azole comprising at least one of miconazole, ketoconazole, dichlorophenyl imidazolodioxalan, clotrimazole, itraconazole, econazole, miconazole, climbazole, terconazole, tioconazole, sertaconazole, sulconazole, butoconazole, fluconazole, valconazole, and present in an amount sufficient to prevent TEWL and provide skin barrier protection, zinc oxide and petrolatum along with other ingredients. These compositions provide relief from itching and inflammation, and moisturize the skin as well. They also promote the healing of rashes, numerous skin disorders and types of skin atrophy.

[00013] Accordingly, it is an object of some embodiments of the present invention to provide a composition and method for preventing TEWL.

[00014] It is another object of some embodiments of the present invention to provide a composition and method for improving or promoting moisturization of skin comprising administering an effective amount of at least one azole to an individual in need of such improvement or promotion.

[00015] It is another object of some embodiments of the present invention to provide a composition and method for promoting healing of damaged skin.

[00016] It is a further object of some embodiments of the present invention to provide a composition and method for relieving skin itch.

[00017] The file of this patent contains at least one drawing executed in color. Copies of this patent with color drawing(s) will be provided by the Patent and Trademark Office upon request and payment of the necessary fee.

BRIEF DESCRIPTION OF THE DRAWINGS

[00018] Fig. 1 illustrates the dynamics of skin barrier repair, as measured by reduction in TEWL, after topical application of different skin formulations. TEWL reduction in damaged epidermis (standardized skin stripping in volunteers) was used as a measure of skin barrier protection for the skin formulations. A double blind intra-individual randomized study was conducted in accordance with the declaration of Helsinki and its subsequent amendments at the University of Liege. Fifteen volunteers were enrolled. Rings on the volar aspect of the forearms delimited seven areas of 2 cm² in size. In each subject, an equal number of successive tape strippings (Tartan tape, 19 mm wide) were performed until TEWL reached 15g/cm²/h on all test sites. Measurements were performed using a Tewameter® (C+K electronic, Cologne) according to the EEMCO recommendations (Rogiers V., Skin Pharmacol Appl Skin Physiol 2001; 14: 117-128). One of the test sites was left untreated. Each of the other test sites received 1 mg of either: (1) a medicated paste made of petrolatum, 15% ZnO and 0.25% miconazole nitrate (Zimycan®, Barrier Therapeutics), (2) the miconazole nitrate-free Zimycan® paste (Zimybase®, Barrier Therapeutics) or (3) petrolatum (ZnO-free Zimybase®). Applications were performed twice daily, and TEWL measurements were taken daily 1 h after the morning treatment.

[00019] Fig. 2 illustrates the dynamics of skin barrier repair, as measured by reduction in TEWL, after topical application of different skin formulations. Figure 2 is essentially the same as Figure 1 except that each of the treated test sites received 2 mg/cm² of either: (1) a medicated paste made of petrolatum, 15% ZnO and 0.25% miconazole nitrate (Zimycan®, Barrier Therapeutics), (2) the miconazole nitrate-free Zimycan® paste (Zimybase®, Barrier Therapeutics) or (3) petrolatum (ZnO-free Zimybase®).

DETAILED DESCRIPTION

[00020] Since the skin barrier regulates the rate of water loss from the body, the rate of transepidermal water loss is a measure of the condition of the skin barrier. When skin is damaged, its barrier function is impaired resulting in high water loss.

[00021] Skin barrier alterations exhibit profound negative effects on skin physiology. They can induce microinflammation in the inflammatory cascade. The present invention provides a skin barrier protection composition containing at least an azole derivative, zinc oxide and petrolatum.

[00022] Preferred embodiments of the present invention comprise a combination of miconazole, zinc oxide and petrolatum along with other ingredients. These compositions provide relief from itching and swelling, moisturize skin and promote the healing of rashes and skin disorders.

[00023] The most preferred mode of administration for treating the skin disorders described above is topical. The compounds of the present invention can be formulated into suitable therapeutic, dermatological, pharmaceutical, medical, and/or cosmetic compositions depending on the particular use for which it is to be used. For example, cosmetic or therapeutic, or both.

[00024] The compositions of some embodiments of the present invention may contain additional ingredients such as carrier, solvent, excipient or vehicle ingredients. These may include, by way of example and not by way of limitation, water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1, 3-diol, acrylates copolymers, isopropyl myristate, isopropyl palmitate, mineral oil, butter(s), aloe, talc, botanical oils, botanical juices, botanical extracts, botanical powders, other botanical derivatives, lanolin, urea, petroleum preparations, tar preparations, plant or animal fats, plant or animal oils, soaps, triglycerides, and keratin(s). Mixtures formed by the

combination of the above ingredients to form soaps, lotions, tinctures, creams, pastes, emulsions, gels/jellies, aerosols, sprays or ointments which are non-toxic and pharmaceutically, medically, dermatologically, and/or cosmetically acceptable may also be comprised within embodiments of the present invention.

[00025] Additionally, moisturizers or humectants, sunscreens, fragrances, dyes, thickening agents such as paraffin, jojoba, paba, and waxes, surfactants, occlusives, hygroscopic agents, emulsifiers, emollients, lipid-free cleansers, antioxidants and lipophilic agents, maybe added to the present compositions if desired.

[00026] Moisturizers or humectants are known in the art and include, for example, materials selected from the group consisting of glycerol; guanidine; glycolic acid and glycolate salts (e.g., ammonium and quaternary alkyl ammonium); lactic acid and lactate salts (e.g., ammonium and quaternary alkyl ammonium); aloe vera in any of its variety of forms (e.g., aloe vera gel); polyhydroxy alcohols such as sorbitol, glycerol, hexanetriol, propylene glycol, butylene glycol, hexylene glycol and the like; polyethylene glycols; sugars and starches including sorbitol; sugars and starch derivatives (e.g., alkoxylated glucose); hyaluronic acid; pyrrolidone carboxylic acid; lactamide monoethanolamine; acetamide monoethanolamine; and mixtures thereof

[00027] In addition to these and other vehicles, it shall be understood that the therapeutic, dermatological, pharmaceutical, medical, and/or cosmetic compositions of the present invention may include other ingredients such as those that improve or eradicate itching, irritation, pain, inflammation, age spots, keratoses, wrinkles, and other blemishes or lesions of the skin. By way of example and not by way of limitation, analgesics, anesthetics, antiacne agents, antibacterial agents, anti-yeast agents, anti-fungal agents,

antiviral agents, antibiotic agents, porbiotic agents, anti-protozal agents, anti-pruritic agents, antidandruff agents, anti-dermatitis agents, anti-emetics, anti-inflammatory agents, anti-hyperkeratolytic agents, anti-dry skin agents, antiperspirants, anti-psoriatic agents, anti-seborrheic agents, hair conditioners, hair treatments, hair growth agents, anti-aging agents, anti-wrinkle agents, antihistamine agents, disinfectants, skin lightning agents, depigmenting agents, vitamins and vitamin derivatives, gamma-linolenic acid (GLA), beta carotene, quercetin, asapalene, melalucas altemifolia, dimethicone, neomycin, corticosteroids, tanning agents, sulfur agents, hormones, retinoids, griseofalvin, hydroxyzine, diphenhydramine, pramoxine, lidocaine, procaine, mepivacaine, monobenzene, erythidocaine, erythromycin, tetracycline, clindamycin, meclocline, hydroquinone, minocycline, naproxen, ibuprofen, theophylline, cromolyn, albuterol, retinoic acid and its derivatives, hydrocortisone and its derivatives, mometasone, desonide, trimcinolone, prednisolone, nutracort™, salicylic acid, phospholipids, calamine, allantoin, isohexadelane, ceresin, galcipotriene, dovonex™, anthralin, betamethasone valerate, betamethasone dipropionate, trimcinolone acetate, fluocinonide, clobetasol propionate, benzoyl peroxide, crotamiton, propranolol, promethazine, vitamin A palmitate, vitamin E acetate, vitamin D and mixtures or derivatives thereof may be added to embodiments of the present invention to improve or alter their effectiveness.

[00028] Also, useful are propoxylated glycerols as described in U.S. Pat. No. 4,976,953, to Orr et al., issued Dec. 11, 1990, which is incorporated by reference herein in its entirety. Suitable moisturizers are also disclosed by Loden et al. (1994), "Product Testing--Testing of Moisturizers," in Bioengineering of the Skin: Water and the Stratum Corneum, Elsner et al., eds, CRC Press, Boca Raton, Fla., 275.

[00029] Skin protecting agents are known in the art and are useful herein as a characteristic use agent and include sunscreens, insecticides, insect repellants, anti-acne additives, anti-wrinkle and anti-skin atrophy additives.

[00030] A wide variety of suncreening agents are described in U.S. Pat. No. 5,087,445, to Haffey et al., issued Feb. 11, 1992; U.S. Pat. No. 5,073,372, to Tumer et al., issued Dec. 17, 1991; U.S. Pat. No. 5,073,371, to Turner et al., issued Dec. 17, 1991; and Segarin, et al., at Chapter VIII, pages 189 et seq., of Cosmetic Science and Technology, all of which are incorporated herein by reference in their entirety. Nonlimiting examples of sunscreens which are useful in the compositions of the present invention are those selected from the group consisting of 2-ethylhexyl p-methoxycinnamate, 2-ethylhexyl N,N-dimethyl-p-aminobenzoate, p-aminobenzoic acid, 2-phenylbenzimidazole-5-sulfonic acid, octocrylene, oxybenzone, homomenthyl salicylate, octyl salicylate, 4,4'-methoxy-t-butylidibenzoylmethane, 4-isopropyl dibenzoylmethane, 3-benzylidene camphor, 3-(4-methylbenzylidene) camphor, anthanilates, ultrafine titanium dioxide, zinc oxide, silica and iron oxide and mixtures thereof. Still other useful sunscreens are those disclosed in U.S. Pat. No. 4,937,370, to Sabatelli, issued Jun. 26, 1990; and U.S. Pat. No. 4,999,186, to Sabatelli et al., issued Mar. 12, 1991; these two references are incorporated by reference herein in their entirety. The sunscreening agents disclosed therein have, in a single molecule, two distinct chromophore moieties, which exhibit different ultraviolet radiation absorption spectra. One of the chromophore moieties absorbs predominantly in the UVB radiation range and the other absorbs strongly in the UVA radiation range. These sunscreening agents provide higher efficacy, broader UV absorption, lower skin penetration and longer lasting efficacy relative to conventional sunscreens. Examples of these sunscreens include those selected from the

group consisting of 4-N,N-(2-ethylhexyl)methylaminobenzoic acid ester of 2,4-dihydroxybenzophenone, 4-N,N-(2-ethylhexyl)-methylaminobenzoic acid ester with 4-hydroxydibenzoylmethane, 4-N,N-(2-ethylhexyl)-methylaminobenzoic acid ester of 2-hydroxy-4-(2-hydroxyethoxy)benzophenone, 4-N,N(2-ethylhexyl)-methylaminobenzoic acid ester of 4-(2-hydroxyethoxy)dibenzoylmethane, and mixtures thereof.

[00031] Nonlimiting examples of anti-wrinkle and anti-skin atrophy actives include retinoic acid and its derivatives (e.g., cis and trans); retinol, retinyl esters, salicylic acid and derivatives thereof; sulfur-containing D and L amino acids other than cysteine and their derivatives and salts, particularly the N-acetyl derivatives; alpha-hydroxy acids, e.g., glycolic acid, and lactic acid; phytic acid, lipoic acid, lysophosphatidic acid, and skin peel agents (e.g., phenol and the like).

[00032] Nonlimiting examples of insecticides, insect repellants and anti-arthropod agents include N,N-diethyl-m-toluamide, N-aryl and N-cycloalkyl neoalkonamide compounds as described in U.S. Pat. No. 5,434,190 incorporated by reference herein, terpenoids, especially terpenoid alcohols and terpenoid-esters, aldehyde and ketones of terpenes as described in U.S. Pat. No. 5,411,992 incorporated by reference herein, oils of citronella, cedar and wintergreen as described in U.S. Pat. No. 5,106,622 incorporated by reference herein, 1-nonen-3-ol, and pyrethrum/pyrethroids as described in U.S. Pat. No. 4,668,666 incorporated by reference herein.

[00033] Antibacterial agents such as antibiotics and bactericides, and fungicides are known in the art and are useful herein as a characteristic use agent. Nonlimiting examples of useful antibacterial agents and fungicides include, β -lactam drugs, quinolone drugs, ciprofloxacin, norfloxacin, tetracycline, erythromycin, amikacin, 2,4,4'-trichloro-2'-hydroxy diphenyl ether, 3,4,4'-trichlorobanilide,

phenoxyethanol, phenoxy propanol, phenoxyisopropanol, doxycycline, capreomycin, chlorhexidine, chloretracycline, oxytetracycline, clindamycin, ethambutol, hexamidine isethionate, metronidazole, pentamidine, gentamicin, kanamycin, lineomycin, methacycline, methenamine, minocycline, neomycin, netilmicin, paromomycin, streptomycin, tobramycin, miconazole, tetracycline hydrochloride, erythromycin, zinc erythromycin, erythromycin estolate, erythromycin stearate, amikacin sulfate, doxycycline hydrochloride, capreomycin sulfate, chlorhexidine gluconate, chlorhexidine hydrochloride, chlortetracycline, hydrochloride, oxytetracycline hydrochloride, clindamycin hydrochloride, ethambutol hydrochloride, metronidazole hydrochloride, pentamidine hydrochloride, gentamicin sulfate, kanamycin sulfate, lineomycin hydrochloride, methacycline hydrochloride, methenamine hippurate, methenamine mendelate, minocycline hydrochloride, neomycin sulfate, netilmicin sulfate, paromomycin sulfate, streptomycin sulfate, tobramycin sulfate, miconazole hydrochloride, amanfadine hydrochloride, amanfadine sulfate, octopirox, parachlorometa xyleneol, nystatin, tolnaftate and clotrimazole.

[00034] Skin lightening agents are known in the art and are useful herein as a characteristic use agent. Nonlimiting examples of useful skin lightening agents include glycosides of hydroxysalicylic acid and/or the glycosides of aliphatic esters of hydroxysalicylic acid as described in U.S. Pat. No. 5,700,784 incorporated by reference herein, hydroquinone, kojic acid or a derivative thereof, especially the salts or esters thereof as described in U.S. Pat. No. 5,279,834 incorporated by reference herein, 3-hydroxy-4(H)-pyran-4-one and its 3-acyl derivatives as described in U.S. Pat. No. 4,545,982 incorporated by reference herein, and 4-hydroxy-5-methyl-3[2H]-furanone.

[00035] Artificial tanning agents and accelerators are known in the art and are useful herein as a characteristic use agent. Nonlimiting examples of useful artificial tanning agents and accelerators include dihydroxyacetone, tyrosine, tyrosine esters such as ethyl tyrosinate, and phospho-DOPA.

[00036] Anti-acne actives are known in the art and are useful herein as a characteristic use agent. Nonlimiting examples of useful anti-acne actives include the keratolytics such as salicylic acid (o-hydroxy-benzoic acid), derivatives of salicylic acid such as 5-octanoyl salicylic acid, and resorcinol; retinoids such as retinoic acid and its derivatives (e.g., cis and trans); sulfur-containing D and L amino acids other than cysteine and their derivatives and salts, particularly their N-acetyl derivatives; lipoic acid; antibiotics and antimicrobials such as benzoyl peroxide, octopirox, tetracycline, 2,4,4'-trichloro-2'-hydroxydiphenyl ether, 3,4,4'-trichlorobanilide, azelaic acid and its derivatives, phenoxyethanol, phenoxypropanol, phenoxisopropanol, ethyl acetate, clindamycin and melclocycline; sebostats such as flavonoids; and bile salts such as scymnol sulfate and its derivatives, deoxycholate, and cholate. Antiviral agents are also known in the art and useful herein as a characteristic use agent. Nonlimiting examples of antiviral agents include acyclovir, vidarabine, penciclovir, trifluridine, idoxuridine, podophyllotoxin and carbenoxolone.

[00037] The compounds of the present invention may be used as their therapeutic, dermatological, pharmaceutical, medical, and/or cosmetic acceptable salts. Such salts may be prepared from pharmaceutically and chemically acceptable non-toxic acids or bases including inorganic and organic acids and inorganic and organic bases. Such salts may contain, by way of example and not by way of limitation, the following ions: Acetate, benzensulfonate, benzoate, camphorsulfonate, citrate, fumarate, gluconate, hydrobromide, hydrochloride, lactate,

maleate, mandelate, mucate, nitrate, pamoate, phosphate, succinate, sulfate, tartate, pyruvate and the like. Such salts may also contain the following cations: aluminum, calcium, lithium, magnesium, potassium, sodium, zinc, benzathine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine and procaine.

[00038] One preferred type of skin barrier protective composition includes those therapeutic components that are effective in the treatment of dandruff, seborrheic dermatitis, and psoriasis as well as the symptoms associated therewith. Examples of such suitable skin barrier protective compositions nonexclusively include, imidazoles such as miconazole, ketoconazole, dichlorophenyl imidazolodioxalan, which is commercially available from Janssen Pharmaceutica, N. V., under the tradename, "Elubiol", clotrimazole, itraconazole, econazole, miconazole, climbazole, terconazole, tioconazole, sertaconazole, sulconazole, butoconazole, fluconazole and valconazole and any possible stereo isomers and derivatives thereof.

[00039] In a preferred embodiment in which the active component is miconazole, a suitable amount of miconazole is, based upon the total weight of composition, from greater than about 0.1 percent to about 10 percent, more preferably from about 0.1 percent to about 2 percent and most preferably from about 0.25 percent to about 2 percent.

[00040] The composition of this invention can be formulated in a variety of dosage forms for topical application that include, but are not limited to, for example, lotions, creams, ointments, sprays, aerosols, skin patches, soap, mousses, tonics, gels or the like which is designed to be left on the skin and not washed shortly after application. Alternatively, the composition may be applied to the desired area in the form of, for example, a lotion, cream, gel, soap, shampoo or the

like which is designed to be rinsed off within a given amount of time after application.

[00041] Another embodiment of the present invention is directed to a method for enhancing the topical application of skin barrier protective compositions, which comprises topically administering to a human or animal a composition as described above.

[00042] While the amount of skin barrier protective composition to be applied will depend upon, for example, the intended usage of the final composition, i.e. therapeutic versus maintenance regimen, and sensitivity of the individual user to the composition, typically the composition of the present invention should be topically applied to affected body parts at regular intervals, and preferably from about 5 to about 7 times per week. More preferably, the composition is applied more frequently during the initial stages of treatment, e.g. from twice daily until the desired effect is achieved, then less frequently when maintenance is desired, e.g. from about 3 to about 5 times per week.

[00043] In a preferred embodiment wherein the composition is incorporated into a shampoo, the shampoo is applied to wet hair, and the hair is washed in accordance with known practices. More preferably, the composition remains on the hair for greater than about 0 to about 10 minutes, and preferably from about 4 to about 7 minutes before rinsing.

[00044] Another preferred embodiment of the present invention is directed to a method for treating acne and for reducing the signs of aging, i.e. wrinkles, fine lines, and other manifestations of photodamage, comprising topically applying to skin at a desired area the above-described composition, e.g. the combination of non-ionic lipid and vehicle solution, containing an anti-acne agent or an anti-aging agent, respectively.

[00045] Examples of suitable anti-aging agents include, but are not limited to inorganic sunscreens such as titanium dioxide and zinc oxide; organic sunscreens such as octyl-methyl cinnamates and derivatives thereof; retinoids; vitamins such as vitamin E, vitamin A, vitamin C, vitamin B, and derivatives thereof such as vitamin E acetate, vitamin C palmitate, and the like; antioxidants including alpha hydroxy acid such as glycolic acid, citric acid, lactic acid, malic acid, mandelic acid, ascorbic acid, alpha-hydroxybutyric acid, alpha-hydroxyisobutyric acid, alpha-hydroxyisocaproic acid, atrolactic acid, alpha-hydroxyisovaleric acid, ethyl pyruvate, galacturonic acid, glucopehonic acid, glucopheptono 1,4-lactone, gluconic acid, gluconolactone, glucuronic acid, glucuronolactone, glycolic acid, isopropyl pyruvate, methyl pyruvate, mucic acid, pyruvic acid, saccharic acid, saccharic acid 1,4-lactone, tartaric acid, and tartronic acid; beta hydroxy acids such as beta-hydroxybutyric acid, beta-phenyl-lactic acid, beta-phenylpyruvic acid; botanical extracts such as green tea, soy, milk thistle, algae, aloe, angelica, bitter orange, coffee, goldthread, grapefruit, hoellen, honeysuckle, Job's tears, lithospermum, mulberry, peony, pueraria, rice, safflower, and mixtures thereof. Preferred anti-aging agents include retinoids, anti-oxidants, alpha-hydroxy acids and beta-hydroxy acid with retinol and tretinoin being most preferred.

[00046] Examples of suitable anti-acne agents include, but are not limited to topical retinoids (tretinoin, Isotretinoin, Motretinide, Adapalene, Tazarotene, Azelaic acid, retinol); salicylic acid; benzoyl peroxide; antibiotics such as tetracycline and isomers thereof, erythromycin, and the anti-inflammatory agents such as ibuprofen, naproxen, ketoprofen; botanical extracts such as alnus, arnica, artemisia capillaris, asiaticum root, birch, calendula, chamomile, cnidium, comfrey, fennel, galla rhois, hawthorn, houttuynia,

hypericum, jujube, kiwi, licorice, magnolia, olive, peppermint, philodendron, salvia, sasa albo-marginata; imidazoles such as ketoconazole and elubiol, and those described in Gollnick et al., ((1998) Dermatology Sebaceous Glands, Acne and Related Disorders, 196(1):119-157)), which is incorporated by reference herein, and mixtures thereof. Preferred anti-acne agents include retinol, elubiol, antibiotics, and salicylic acid, with retinol and tretinoin being most preferred.

[00047] Suitable amounts of anti-aging agents include, based upon the total weight of the composition, from about 0.01 percent to about 10 percent, and preferably from about 0.04 percent to about 5 percent. Suitable amount of anti-acne agents include, based upon the total weight of the composition, from about 0.01 percent to about 10 percent, and preferably from about 0.04 percent to about 5 percent.

[00048] It has been found that the transdermal penetration of a given pharmacologically active compound can be substantially improved by incorporating into a composition containing said pharamacologically active compound a transdermal penetration enhancing amount of imidazole or an imidazole derivative.

[00049] This unexpected effect is quite useful in that it allows one to improve the transdermal delivery of the pharmacologically active compound from the composition, thereby allowing one to achieve the same level of efficacy with a lower overall concentration of the pharmacologically active compound in the composition.

[00050] The present invention provides skin barrier protection compositions that also provide transdermal penetration effect for delivery of various pharmacologically active agents into and through the skin. Such pharmacologically active agents include, but are not limited to, antihistamines, such as for example tripelennamine,

triprolidine, diphenhydramine and, chlorpheniramine, all of which may be employed either as the free base or as a pharmaceutically acceptable salt.

[00051] In addition to antihistamines, other pharmacologically active agents may also have their skin penetration enhanced by the method of the present invention. Such agents include but are not limited to, the following:

[00052] Anti-bacterials; deodorants; anti-ulcer, antispasmodic and other drugs effecting the gastrointestinal tract; NSAIDS (such as for example aspirin and ibuprofen); analgesics (such as for example aspirin and ibuprofen); antipyretics, anti-inflammatories (such as for example aspirin and ibuprofen); steroids; (such as for example prednisone, prednisolone and hydrocortisone and pharmaceutically acceptable salts thereof) antifungal agents; antihypertensive agents; sympathomimetic amines (such as for example xylometazoline, phenylephrine, naphazoline and metaproterenol); central nervous system active agents; diuretics (such as for example hydrochlorothiazide); antitussives (such as for example dextromethorphan); vasodilators (such as for example nitroglycerin); anti-nauseants; and compounds for treating motion sickness.

[00053] Certain of the imidazole and imidazole derivatives disclosed herein as enhancing the transdermal penetration of pharmacologically active agents can penetrate to an extent sufficient to exert their own pharmacological effect. Xylometazoline and naphazoline are prime examples of this.

[00054] Normally, the pharmacologically active agent and the imidazole or imidazole derivative will be present in an aqueous vehicle containing an emollient and a surfactant in amounts which will be dictated by dosage considerations and the conditions of intended use, all of which are within the ability of one skilled in the art to determine and therefore will not be described in further detail here.

[00055] In the preferred embodiment the compositions will preferentially contain up to about 5.0 wt. % of pharmacologically active agent and from about 0.5 wt. % up to about 5.0 wt. % of imidazole or imidazole derivative, based upon the total weight of the prepared composition.

[00056] More preferably, from about 0.05 wt. % to about 3.0 wt. % imidazole or imidazole derivative will be present and most preferably from about 0.25 wt. % to about 1.0 wt. % will be used. Typically 0.25 wt. % of imidazole or imidazole derivative will be adequate to achieve enhanced penetration.

[00057] While the invention has generally been described above, the details of the present invention will be better understood by recourse to the examples, which follow.

[00058] Example 1:

Preferred embodiments of the present invention comprise the following ingredients, which are listed according to their percentage by weight in relation to the total weight of the composition.

[00059] Skin barrier disruption coincides with an increase in TEWL. The recovery rate to normal values of TEWL following tape stripping is a good marker for assessing the skin barrier recovery. The following example was used to compare the effect of two topical pastes (petrolatum, zinc oxide with or without miconazole nitrate), and petrolatum alone on impaired skin barrier function.

[00060] The aim of the present study was to assess the effects of paste-derived topical formulations on skin barrier repair after controlled tape strippings. Attention was paid to the amount of the products applied to the compromised skin, and to the influence if any of miconazole nitrate incorporated in the formulations.

[00061] This single-blind, randomized intra-individual study was conducted in accordance with the declaration of Helsinki and its subsequent amendments. Fifteen volunteers aged from 34 to 48 years were enrolled after they signed an informed consent. Rings on the volar aspect of the forearms delimited seven areas of 2 cm² in size. In each subject, an equal number of successive tape strippings (Tartan tape, 19 mm wide) were performed until TEWL reached 15g/cm²/h on all test sites. One of the test sites was left untreated. Each of the other test sites received 1 of 3 formulations, which was applied twice daily for 5 days on distinct randomized test sites. The 3 formulations were (1) 1 mg or 2mg/cm² of either a medicated paste made of petrolatum, 15% ZnO and 0.25% miconazole nitrate (Zimykan®, Barrier Therapeutics), (2) the 0.25% miconazole nitrate-free Zimykan® paste (Zimybase®, Barrier Therapeutics) or (3) petrolatum (ZnO-free Zimybase®). A nurse performed

applications twice daily. TEWL measurements were taken at baseline (D0) and daily for 4 days, each time 1 hour after the morning applications. The experimenter was unaware of the product randomization. A fastened skin barrier repair was induced by the 3 formulations. The effect was significantly more intense for each preparation where the largest amount had been applied. (Tables 1-4; Figures 1 and 2). No difference was yielded between petrolatum and the unmedicated paste. The paste containing miconazole nitrate obtained the faster recovery rate. The occlusive effect of petrolatum and a regular paste with zinc oxide help mitigating skin barrier defect. The adjunction of miconazole nitrate improves the efficacy.

[00062]

TABLE 1
TEWL-UNTREATED

VOLUNTEER	INCLUSION	D1	D2	D3	D4
1	16.3	17.2	16.1	14.7	12.2
2	17.7	15.8	13.4	11.8	8.7
3	16.8	16.5	15.2	15.3	13.8
4	19.2	21.3	18.5	16.0	14.1
5	15.9	14.7	11.0	8.7	6.5
6	17.4	17.2	16.2	15.0	13.1
7	16.2	16.5	15.4	15.8	15.3
8	18.6	17.9	17.1	16.0	14.1
9	19.2	18.5	16.9	14.5	11.5
10	18.0	16.3	16.1	13.9	10.2
11	16.8	13.2	11.4	9.9	8.6
12	16.2	15.8	13.9	12.6	10.0
13	15.7	11.8	9.6	7.7	6.1
14	19.1	20.3	18.9	16.2	16.3
15	18.3	16.1	14.9	11.5	8.8
MEAN	17.43	16.61	14.97	13.31	11.29
SD	1.25	2.41	2.69	2.80	3.17
MEDIAN	17.40	16.50	15.40	14.50	11.50

[00063]

TABLE 2
TEWL-ZIMYBASE® 1 mg/cm²

VOLUNTEER	INCLUSION	D1	D2	D3	D4
1	16.2	10.5	12.7	6.4	8.5
2	16.5	11.8	8.4	7.9	6.7
3	17.1	8.7	9.2	8.5	8.5
4	16.9	12.9	13.4	8.3	8.1
5	16.3	11.7	8.3	7.5	7.0
6	16.7	10.0	9.6	9.3	9.1
7	16.5	8.9	7.0	6.5	6.6
8	17.7	13.9	11.6	9.9	9.0
9	17.9	10.8	9.8	8.7	9.2
10	16.7	13.2	11.7	9.8	9.1
11	16.5	11.8	9.5	9.3	8.6
12	16.7	13.3	10.1	9.7	6.6
13	16.4	11.0	10.5	10.3	8.4
14	17.5	13.9	10.7	9.8	6.1
15	18.0	11.4	11.8	8.3	6.9
MEAN	16.91	11.59	10.29	8.68	7.89
SD	0.59	1.65	1.74	1.22	1.11
MEDIAN	16.70	11.70	10.10	8.70	8.40

[00064]

TABLE 3
TEWL-ZIMYCAN® 1 mg/cm²

VOLUNTEER	INCLUSION	D1	D2	D3	D4
1	16.8	11.7	11.5	9.9	7.9
2	17.4	10.6	8.2	7.7	6.1
3	16.3	12.9	10.6	9.3	8.0
4	18.2	15.5	14.2	14.1	10.2
5	16.7	10.2	8.4	6.1	4.4
6	16.3	8.3	12.5	8.1	7.5
7	16.6	9.8	6.6	3.2	3.8
8	18.7	10.4	8.2	7.6	7.7
9	18.5	14.3	11.3	9.8	8.4
10	17.2	8.5	9.2	6.4	8.3
11	17.4	11.4	7.7	7.5	7.9
12	16.0	14.2	10.5	6.3	4.0
13	15.5	8.6	11.7	2.8	6.7
14	17.6	14.3	11.9	6.7	3.8
15	17.9	9.9	6.1	3.5	3.2
MEAN	17.14	11.37	9.91	7.27	6.53
SD	0.94	2.35	2.34	2.92	2.16
MEDIAN	17.20	10.60	10.50	7.50	7.50

[00065]

TABLE 4
TEWL-ZIMYCAN® 2 mg/cm2

VOLUNTEER	INCLUSION	D1	D2	D3	D4
1	16.6	6.3	6.6	1.4	4.9
2	17.0	5.2	4.7	4.9	4.5
3	16.6	8.5	3.2	2.8	2.8
4	17.9	7.0	8.7	3.3	1.0
5	16.5	4.4	2.9	2.6	2.3
6	17.0	8.3	5.0	3.3	3.7
7	16.0	6.3	4.1	4.0	3.0
8	18.2	9.4	1.3	2.4	2.1
9	18.3	10.1	4.7	6.3	4.9
10	17.9	9.0	2.8	4.0	1.1
11	16.8	5.1	3.6	4.2	3.3
12	16.3	4.5	2.4	2.1	2.8
13	15.3	6.3	8.4	5.4	5.5
14	18.2	7.2	4.4	7.0	1.9
15	16.3	6.5	6.0	2.2	2.0
MEAN	16.99	6.94	4.59	3.73	3.05
SD	0.91	1.79	2.11	1.62	1.40
MEDIAN	16.80	6.50	4.40	3.30	2.80

[00066] The TEWL evolution (means of 15 human subjects) for the 7 test sites is given in Tables 1-4. Results at baseline for the different treatment sites were summarized as median values. Mixed model analysis of variance of the data obtained at day 1 - 4 with measurements made at the inclusion day (0) as covariate, treatment day as factor and a compound symmetry structure for the covariance matrix, indicated a significant lower TEWL for Zymican® at 2 mg/cm² than for both Zymibase® and ZnO-free Zymibase® (Dunnett-Hsu test, two-sided versus Zymibase® p=0.011, versus ZnO-free Zymibase® p=0.017). No statistically significant difference could be detected between Zymibase® and its ZnO-free version (unadjusted p=0.836). Using the two-sided Dunnett-Hsu test, TEWL in the miconazole group is significantly lower than that for the petrolatum + ZnO group (p = 0.011) and than that for Petrolatum alone

($p = 0.017$). Computations were carried out using the SAS 8.0.2 system for statistical analysis.

[00067] The dynamics of skin barrier repair, as measured by reduction in TEWL, after topical application of the 3 different skin formulations is illustrated in Figures 1 and 2. The additive effects of miconazole are unexpected. Indeed, already in the 1 mg/cm² group, there is a trend towards a significantly improved TEWL in the Petrolatum + ZnO + miconazole group versus the 2 other treatment groups. This difference in favor of the miconazole-containing formulation becomes significant in the groups treated with 2 mg/cm.

[00068] In order to have smooth, hydrated and non-scaly skin, an intact SC barrier function is essential. The assessment of TEWL by evaporimetry or by the passive sustainable hydration test has been shown to be a suitable tool to quantify any impairment of the barrier function (Abrams et al., (1993) J. Invest. Dermatol. 101:609-613; Van Cromphaut et al., (1999) J. Environ. Med. 1:47-50.). This function resides in the SC, which is composed of protein-rich nonviable cells and intercellular lipid domains originating from the keratinosomes. When tape stripping or treatment with an organic solvent or detergent damages the SC barrier function, a series of homeostatic processes in barrier function is immediately accelerated, and the barrier recovers to its original level. This process includes lipid synthesis, lipid processing, and the acceleration of exocytosis of lipid-containing lamellar bodies in the upper epidermis.

[00069] In comparison with untreated skin, an improved skin barrier repair was observed after applications of petrolatum and of both the medicated and unmedicated pastes. Furthermore, the miconazole nitrate paste had a somewhat greater protective effect than its unmedicated vehicle. The mechanism of action of miconazole nitrate on this aspect of skin biology is uncertain.

[00070] The present invention provides that the 3 tested formulations decrease TEWL and thus helps in repairing an impaired skin barrier function. The presence of zinc oxide does not appear to influence this effect.

[00071] Based on general knowledge it was expected that petrolatum alone would reduce TEWL in this test model. Adding ZnO to the petrolatum base did not substantially alter/improve the TEWL reduction in the volunteers. It is surprising however, that adding 0.25% miconazole to the petrolatum + ZnO base causes a significant enhancement in TEWL reduction as compared to petrolatum alone and petrolatum + ZnO.

[00072] This TEWL reducing effect of miconazole has not been described before, and suggests that certain members of the azole family (miconazole, ketoconazole, econazole, clotrimazole, isoconazole, tioconazole, sulconazole, sertaconazole and others) have, in addition to their antifungal effects, also skin barrier enhancing effects.

[00073] The data disclosed herein show that azole derivatives like miconazole have skin barrier protective effects on top of the protective effects of conventional barrier creams. It is believed that, in addition to the antimicrobial effects of the azole moiety, this chemical group also affects the restoration of the barrier protective properties of the epidermis. It is a further aspect of the invention that other azoles for topical use for example, imidazoles such as ketoconazole, dichlorophenyl imidazolodioxalan, clotrimazole, itraconazole, econazole, miconazole, climbazole, terconazole, tioconazole, sertaconazole, sulconazole, butoconazole, fluconazole, valconazole and any possible stereo isomers and derivatives thereof have similar effects to miconazole. This could be important for the development of new topical medications for the treatment of erosive skin lesions, burns, chronic wounds

and wet inflammatory skin conditions such as flexural atopic dermatitis.

[00074] As expected, petrolatum reduces TEWL in a dose dependent manner. Surprisingly, adding ZnO to the petrolatum does not cause a further improvement in TEWL, despite the increase in skin adhesivity that can be observed in the treated volunteers. Finally, adding miconazole in a relatively small concentration (0.25%) shows a surprising enhancement of the TEWL reducing effects of petrolatum.

[0001] Azoles such as miconazole may constitute a novel class of chemicals for treatment of an impaired skin barrier function.

[0002] All publications cited in the specification are indicative of the level of skill of those skilled in the art to which this invention pertains. All these publications are herein incorporated by reference to the same extent as if each individual publication were specifically and individually indicated to be incorporated by reference.

[0010] Although the invention herein has been described with reference to particular embodiments, it is to be understood that these embodiments are merely illustrative of the principles and applications of the present invention. It is therefore to be understood that numerous modifications may be made to the illustrative embodiments and that other arrangements may be devised without departing from the spirit and scope of the present invention as defined by the appended claims.

CLAIMS

1. A method for decreasing transepidermal water loss of skin comprising administering an effective amount of at least one azole derivative to an individual in need thereof.

2. The method of claim 1 wherein the azole derivative is selected from the group consisting of miconazole, ketoconazole, dichlorophenyl imidazolodioxalan, clotrimazole, itraconazole, econazole, miconazole, climbazole, terconazole, tioconazole, sertaconazole, sulconazole, butoconazole, fluconazole and valconazole.

3. The method of claim 2 wherein the effective amount of the azole derivative is about 0.1% to about 10.0%.

4. The method of claim 3 wherein the effective amount of the azole derivative is about 0.25% to about 2.0%.

5. A method for improving or promoting moisturization of skin comprising administering an effective amount of at least one azole to an individual in need of such improvement or promotion.

6. The method of claim 5 wherein the azole derivative is selected from the group consisting of miconazole, ketoconazole, dichlorophenyl imidazolodioxalan, clotrimazole, itraconazole, econazole, miconazole, climbazole, terconazole, tioconazole, sertaconazole, sulconazole, butoconazole, fluconazole and valconazole.

7. The method of claim 6 wherein the effective amount of the azole derivative is about 0.1% to about 10.0%.

8. The method of claim 7 wherein the effective amount of the azole derivative is about 0.25% to about 2.0%.

ABSTRACT OF THE DISCLOSURE

The present invention relates generally to the field of skin care products and more particularly to topical skin applications containing azole derivatives for treatment and prevention of transepidermal water loss. The present invention may be embodied in creams, lotions, oils, sprays and other typical dosage forms for direct application to the skin.

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Dynamics of Skin Barrier Repair after Topical Application

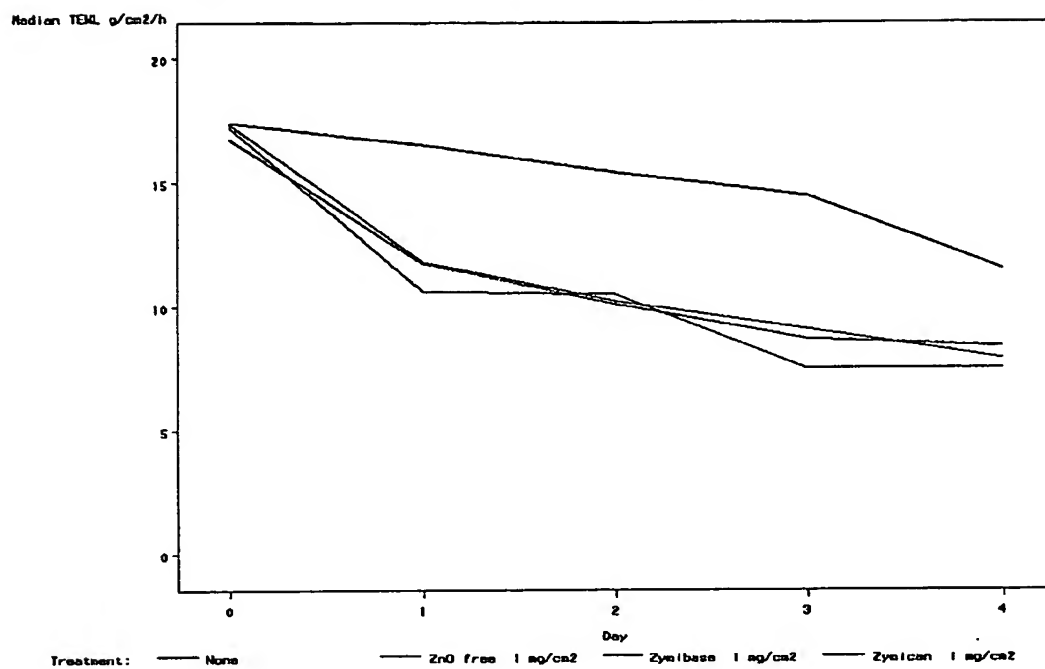


Figure 1

Dynamics of Skin Barrier Repair after Topical Application

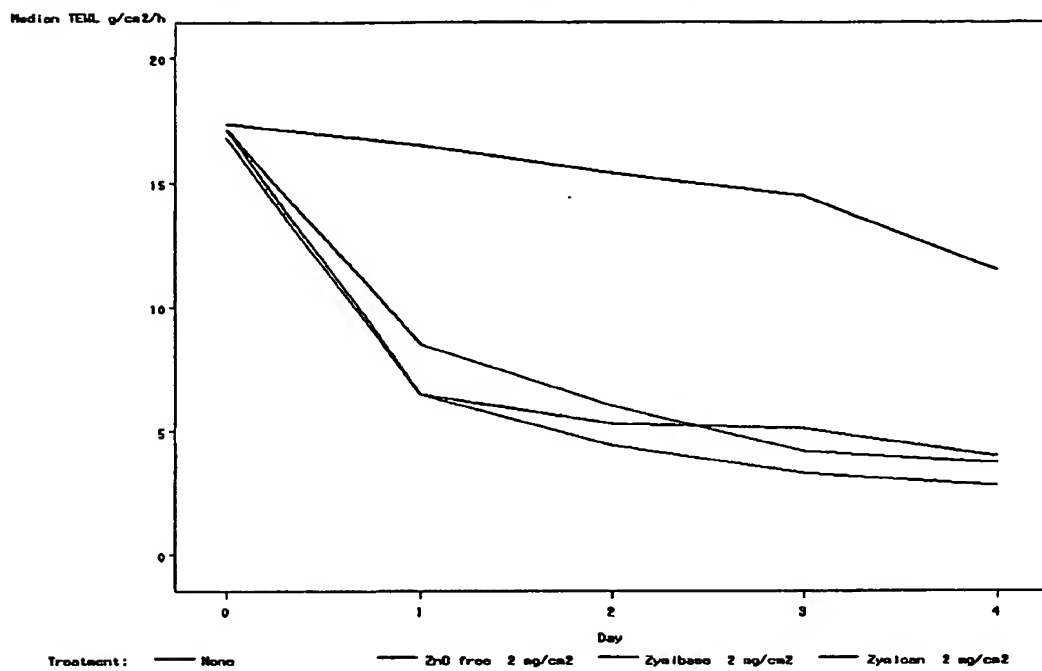


Figure 2

Application Data Sheet

Application Information

Application Type::	Regular
Subject Matter::	Utility
Suggested Group Art Unit::	N/A
CD-ROM or CD-R?::	None
Number of CD disks::	0
Number of copies of CDs::	0
Sequence submission?::	None
Computer Readable Form (CRF)?::	No
Number of copies of CRF::	0
Title::	METHODS FOR TREATING TRANSEPIDERMAL WATER LOSS
Attorney Docket Number::	BTI 1.0-002
Request for Early Publication?::	No
Request for Non-Publication?::	No
Suggested Drawing Figure::	1
Total Drawing Sheets::	2
Small Entity?::	No
Petition included?::	No
Secrecy Order in Parent Appl.?::	No

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